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(11)

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/479,038	06/07/95	DROHAN	W 1327.0440006

EXAMINER	
ZEMAN, M	
ART UNIT	**PAPER NUMBER**
1643	22

HM12/0223
STERNE KESSLER GOLDSTEIN AND FOX
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DATE MAILED: 02/23/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

Responsive to communication(s) filed on 4/30/98 & 11/30/98

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

ıortened statutory period for response to this action is set to expire - 3 - month(s), or thirty days, :hever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 16(a).

ɔosition of Claims

Claim(s) 12, 13, 17-20, 24-32 & 34-37 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
Claim(s) _____ is/are allowed.
Claim(s) 12, 13, 17-20, 24-32 & 34-37 is/are rejected.
Claim(s) _____ is/are objected to.
Claim(s) _____ are subject to restriction or election requirement.

ılication Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
The drawing(s) filed on _____ is/are objected to by the Examiner.
The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
The specification is objected to by the Examiner.
The oath or declaration is objected to by the Examiner.

rity under 35 U.S.C. § 119

Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

] All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

Certified copies not received: _____.

Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

chment(s)

Notice of Reference Cited, PTO-892
Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
Interview Summary, PTO-413
Notice of Draftperson's Patent Drawing Review, PTO-948
Notice of Informal Patent Application, PTO-152

DETAILED ACTION

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 11/30/98 has been entered. Also, the previously unentered After Final amendment, filed 4/30/98 has been entered and considered.

2. Claims 1-13, 17-32, and 34-37 are pending in this application. Claims 1-12 and 21-23 have been withdrawn from consideration as being drawn to a non-elected invention.

3. As set forth in the advisory action mailed 5/22/98, the following rejections have been overcome:

a. The rejection under 35 U.S.C. 103 as unpatentable over Weiner is withdrawn.

b. The rejection under 35 U.S.C. 102(b) over JP 60-204725 is withdrawn.

c. The rejection under 35 U.S.C. 102(e) over Khadem (US Patent 5,552,452) is withdrawn.

d. The rejection under 35 U.S.C. 102 (e) over Gristina (US Patent 5,505,945) is withdrawn.

e. The rejection under 35 U.S.C. 102(a) over WO 92/17206 is withdrawn.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 12, 13, 17-20, 24-32 and 34-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims of copending Application No. 08/485,883. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are directed to fibrin sealant systems which deliver various supplements or medicaments.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 12, 13, 17-20, 24-32 and 34-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims of copending Application No. 08/474,086. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are directed to fibrin sealant systems which deliver various supplements or medicaments.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 12, 13, 17-20, 24-32 and 34-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims of copending Application No. 08/474,084. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are directed to fibrin sealant systems which deliver various supplements or medicaments.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

8. Claims 12, 13, 17-20, 24-32 and 34-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 34 and 36 recite, and Claim 12 has been amended to recite that the matrix can comprise Fibrinopeptide A **or** Fibrinopeptide B. The specification, as filed, does not indicate that a fibrin matrix can form using only one Fibrinopeptide or the other. From a perusal of the art it appears that both fragments of fibrin must be present for a proper matrix to form. This limitation is new matter and must be canceled in response to this rejection.

Applicant has amended claims 18 and 35 to recite that the supplement "retards the degradation" of the fibrin matrix whether through interaction with the fibrin matrix itself or the "external environment". There is not clear support in the specification as filed to support this limitation.

Claims 34 and 36 set forth "anti-angiogenic" compounds. The specification has literal support for "antiangiogenins" which are not necessarily anti-angiogenic.

9. Claims 12, 13, 17-20, 24-32 and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 12, 34 and 36, the metes and bounds of the term "suitable conditions" are unclear, as the nature of those conditions is not clearly set forth in the specification for each claimed species.

The terms "sustained period", and "sustained release", as set forth in claims 12, 34 and 36 and others, are relative terms without a clear defined meaning set forth in the specification for each species or type of supplement claimed. Depending on the context of application, sustained release can be the release of a compound over 3 hours, 3 days, 3 months or 3 years. The release kinetics can also be influenced by chemical interactions of the supplement with components of the fibrin matrix. The specification does not set forth a clear definition of Applicant's intended meaning of these phrases. Applicant has submitted copies of slides from a previous interview of a number of related cases purporting to show the difference between Applicant's sustained release

formulations and that of the art, however these copies are without individual explanation as to their relevance.

In claims 18 and 35, is recited that the supplement must retard the degradation of the fibrin matrix, however, it has not been shown that *each* of the supplements recited in the claims from which claims 18 and 35 depend (namely 12 and 34) acts in such a manner to retard the degradation of the matrix. Further, the retardation of the degradation of the matrix is a subjective measurement for which adequate guidelines are not presented in the specification. The persistence of the supplemented matrix for one day or one hundred days can be interpreted as not being degraded, in comparison to a matrix that is immediately dissolved.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

As to the rejections made under 35 U.S.C. 102 and 103, Applicant has not further defined or limited the metes and bounds of the "sustained release" limitation in the pending claims, nor has Applicant's "sustained release" preparations been sufficiently distinguished from those of the prior

art, consequently the art rejections of record are maintained. Applicant continuously relies upon the argument that none of the art suggests that a supplement be incorporated at a level greater than it is soluble, but it would appear to be a routine optimization of known parameters to adjust the levels of a supplement depending on the dose desired, and the length of time one wished to have the supplement administered in the subject. Applicant has indicated in other copending applications that a declaration discussing the compositions of the invention in comparison to the art pursuant to the interview held 7/30/98 would be forthcoming, however such a declaration is still not of record. In at least one copending application Applicant has submitted copies of slides from that interview, but such slides are not discussed individually as to what they describe and their relevance to the art rejections. Until such declaration is of record, it is impossible for the office to determine whether the compositions of the art are different from that of the invention based upon the specification as filed.

11. Claims 12, 13, 17-20, 29, and 34-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Cadoni.

In regard to Cadoni et al. (Endoscopy 1990 22 p194-195) Applicant's arguments are not persuasive. Cadoni discloses a delivery system for administering an antibiotic slowly over several days. (see p 194, column 2, third full paragraph.) Whether further antibiotic solutions were used in Cadoni is not germane to the claims as currently pending, as the claims do not recite that methods for delivering supplements which exclude the use of other preparations.

Cadoni et al. (Cadoni et al 1990 Endoscopy 22 p 194-195) discloses the use of fibrin sealants comprising an antimicrobial for the treatment of fistula within the duodenum. The antibiotic is released locally over several days.

12. Claims 12-13, 17-20, and 29-32 and 34-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Sakurai.

Claims 29-33 specify that the supplement is an antimicrobial, that the composition comprises thrombin, factor XIII, and calcium, and is administered by a carrier in a solid form.

Sakurai (J Cont. Release 1992 18 p39-44) discloses controlled release of an antibiotic from a fibrin matrix. The examiner notes on the record that Applicant admits that Sakurai is prior art against at least some of the pending claims. Sakurai et al (Sakurai et al 1992 J Controlled Release 18 p 39-44) disclose an implantable composition comprising fibrin, an antimicrobial, thrombin, factor XIII, calcium and other ingredients formed as a disk covered by Dacron. This composition allowed sustained local release of the antimicrobial.

13. Claims 12, 13, 17-20, and 29-32 and 34-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Greco et al..

Applicant attempts to predate Greco (J Biomed Materials 1991 25 p39-51) but does not submit evidence that Applicant's had reduced the invention to practice prior to the publication of Greco. The priority bring claimed is to an application filed in November, 1991. Greco was published in January of 1991. Greco (Greco et al. 1991 J biomedical Materials Research vol 25 p 39-51) disclose compositions comprising fibrin matrices and a variety of antimicrobials including:

Carbenicillin, Gentamicin, Clindamycin, Ampicillin, Tobramycin, Ceftazydime, Cefotaxim and Mezlocillin. These compositions also comprised thrombin, factor XIII, and calcium. These matrices could be implanted and offered local sustained release of those antibiotics.

14. Claims 12-13, 17-20, 30-32 and 34-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Lontz.

Applicant attempts to predate Lontz (US Patent 5,420,250) however, Lontz also has priority under 35 U.S.C. 120 to applications filed in 1990. Applicant points to exemplary portions of the *present* specification to support its claim for priority, and does not indicate where the same support can be found in other parent applications. Lontz teaches the addition of glycoproteins, polysaccharides, and numerous other entities to the fibrin matrix for controlled release. At column 5 Lontz discusses some of the components "The associated plasma macromolecular proteins... characterized as glycoproteins... are intended to be retained as component portions of the {compositions)." The addition of other polysaccharides strengthen the fibrin matrix. Applicant has not indicated which species (ie polysaccharides) are entitled to the priority dates, including the new species, which include "cardiovascular drugs". Lontz discloses fibrin matrices comprising polysaccharides and glycoproteins. Antibiotics and other biomedical entities can be included. These compositions can offer localized sustained release of the included compounds.

15. Claims 12, 13, 17-20 and 29-32 and 34-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Stroetmann.

Applicant asserts that Stroetmann (US Patent 4,427,651)does not set forth the invention as claimed. Applicant's arguments are not persuasive as Stroetmann sets forth a composition comprising large quantities of powdered antibiotic and the components of a fibrin matrix that form said matrix upon application and liquification of the components. Stroetmann (US Patent 4,427,651) discloses fibrin compositions that upon mixing provide a fibrin matrix. These compositions comprise fibrin, thrombin, and thrombolytic inhibitor, and antibiotics as well as calcium. These compositions can provide localized sustained treatment and release of the included compounds.

16. Claims 12, 13, 17-20, 24 and 30-32 and 34-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Luck.

Luck (US Patent 4,619,913) sets forth fibrin matrix compositions which specifically provide for formulations of controlled release of supplements. For example, see column 4 lines 37-55. Luck (US Patent 4,619,913) discloses fibrin matrix compositions comprising cytotoxins and chemotherapeutic agents which are to be implanted in a patient. These compositions provide localized sustained release of the cytotoxins.

17. Claims 12, 13, 17-20, and 29-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Wahlig.

Wahlig (US Patent 4,853,225) discloses fibrin matrix compositions comprising a variety of antibiotics to be implanted into a patient for localized controlled release of the antibiotic. Wahlig

sets forth fibrin matrix compositions specifically formed to offer delayed release of chemotherapeutics.

18. Claims 12, 13, 17-20, 25 and 30-32 and 34-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Juergensen.

Applicant attempts to predate Juergensen (US Patent 5,549,904) however fails to point out where in the priority history of the application the addition of enzymes to fibrin matrices, such as those set forth by Juergensen, were introduced. Juergensen discloses fibrin matrices that comprise transglutaminase and transforming growth factor beta, transforming growth factor alpha, insulin-like growth factor, epidermal growth factor, platelet derived growth factor, tumor necrosis factor, fibroblast growth factor, and interleukins (cytokines). Calcium is also included. These compositions are used to treat bone disorders, ligament disorders, muscle disorders and many others. These compositions can be implanted, and provide localized sustained release of the included factors.

19. Claims 12, 13, 17-20 and 24-32 and 34-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Marx.

Applicant attempts to predate Marx (US Patent 5,607,694) which discloses the incorporation of liposome protected drugs into fibrin matrices for extended release of the drug. However, Applicant has not pointed out where in the prosecution history of the application that liposome incorporated bioactive agents were added. Marx discloses fibrin matrix compositions comprising lipids and liposomes in addition to the basic components of thrombin, factor XIII and

calcium. These lipids serve to release bioactive substances over a sustained period of time at the location of the matrix. Marx discloses the addition of immunoglobulins, protease inhibitors, drugs, vitamins, growth factors, hormones, steroids, antibiotics, tumoricidal and tumoristatic compounds, minerals, polysaccharides, anaesthetics, nucleic acids, and polynucleotides.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Juergenson as applied to claims 12, 13, 17-20, 25 and 30-32 and 34-37 above, further in view of Gerhart.

As discussed above, Juergensen (US Patent 5,549,904) discloses fibrin matrix compositions comprising growth factors and other factors for the treatment of bone and cartilage disorders. Applicant attempts to predate Juergensen (US Patent 5,549,904) however fails to point out where in the priority history of the application the addition of enzymes to fibrin matrices, such as those set forth by Juergensen, were introduced. Gerhart (US Patent 5,364,839) discloses the use of protease inhibitors and bone inductive proteins (BMP's 1-7) as well as growth factors in a biodegradable matrix for the treatment of bone and cartilage disorders. Gerhart does not specifically disclose the use of fibrin matrices, but does specify the usefulness of biodegradable

matrices in the practice of the invention. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the bone inductive proteins of Gerhart in the implantable fibrin matrices of Juergensen, as these proteins were shown to be effective in biodegradable matrices for the treatment of bone and cartilage disorders by Gerhart, and the treatment of such disorders is specifically disclosed by the protocols of Juergensen. The inclusion of the bone inductive proteins would have speeded the regeneration of bone in areas in which the matrix had been implanted.

22. Claims 12-20, 26 and 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Juergensen as applied to claims 12, 13, 17-20, 25 and 30-32 and 34-37 above, further in view of Oppermann.

As discussed above, Juergensen (US Patent 5,549,904) discloses fibrin matrix compositions comprising growth factors and other factors for the treatment of bone and cartilage disorders. Applicant attempts to predate Juergensen (US Patent 5,549,904) however fails to point out where in the priority history of the application the addition of enzymes to fibrin matrices, such as those set forth by Juergensen, were introduced. Oppermann (US Patent 5,354,557) discloses osteogenic implants that comprise demineralized bone, bone inducing proteins, and minerals. These implants are supported by a collagen matrix. Oppermann does not specifically disclose the use of fibrin matrices, but does specify the usefulness of biodegradable matrices in the practice of the invention. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the bone incudctive proteins, minerals,

and demineralized bone complexes of Oppermann in the implantable fibrin matrices of Juergensen, as these compositions were shown to be effective in biodegradable matrices for the treatment of bone and cartilage disorders by Oppermann, and the treatment of such disorders is specifically disclosed by the protocols of Juergensen. The inclusion of these compositions would have speeded the regeneration of bone in areas in which the matrix had been implanted.

Conclusion

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 7:30 am and 5:00 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Eisenschenk, can be reached on (703) 308-0452.

The fax number for this Art Unit is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

mkz
February 17, 1999

Frank C. Eisenschenk
Primary Examiner, Group 1600